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Scientific production on the regulation of unregistered medicines in Brazil, the United States, and Europe

A produção científica sobre a regulação de medicamentos sem registro no Brasil, nos Estados Unidos e na Europa

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ABSTRACT

Introduction: The use of unregistered drugs indicates a shift in the regulatory paradigm for innovative medicines by shortening access to drugs that are still in the experimental phase, which also increases uncertainties regarding the risks associated with their use. **Objective:** to identify the characteristics of scientific publications addressing the regulation of unregistered drugs in Brazil, the United States, and Europe. **Method:** This is a descriptive, quantitative study involving bibliometric analysis. A total of 58 studies were selected based on the descriptors and eligibility criteria from the SciELO, Portal Capes, and Web of Science databases. Absolute and relative frequency analyses, as well as averages of the categories listed in the analysis plan, and keyword profiles using VOSviewer® were performed. **Results:** Researchers' interest in this topic has been growing since 2016. Academic production was concentrated in the United States, by original articles with low methodological rigor, and focused on medical journals. Some studies declared conflicts of interest with the pharmaceutical industry. The central themes were "aspects of the regulatory framework for expanded access/compassionate use" and "ethics in the use of unregistered drugs," with the main keywords being: expanded access, efficacy, safety, Covid-19, risk, emergency authorization, and real-world data. **Conclusions:** The regulation of unregistered drugs deserves further exploration through high-quality studies in the field of Public Health, particularly in countries of the global south, with research that focuses on building elements of individual and collective health protection in the regulation of unregistered drugs.

KEYWORDS: Health Regulation and Inspection; Medication Registration; Brazil; US; Europe

RESUMO

Introdução: A utilização de medicamentos sem registro aponta para uma mudança no paradigma regulatório de medicamentos inovadores ao abreviar o acesso a medicamentos ainda em fase experimental, o que também amplia incertezas quanto aos riscos relacionados ao uso desses medicamentos. Até o momento, não foram encontrados trabalhos que investigassem as tendências da produção bibliográfica sobre o tema. **Objetivo:** identificar as características das produções científicas sobre a regulação de medicamentos sem registro no Brasil, nos Estados Unidos e na Europa. **Método:** Estudo descritivo, quantitativo, análise bibliométrica, que selecionou 58 pesquisas a partir de descritores e critérios de elegibilidade nas bases SciELO, Portal Capes e *Web of Science*. Foram realizadas análises de frequências absolutas e relativas, médias das categorias elencadas no plano de análise e perfil das palavras-chave pelo *VOSviewer*®. **Resultados:** O interesse dos pesquisadores sobre o tema tem crescido desde 2016. A produção acadêmica concentrou-se nos Estados Unidos, em artigos originais, de baixo rigor metodológico, centrada em revistas da área médica. Alguns estudos declararam conflitos de interesse com a indústria farmacêutica. As temáticas centrais foram "aspectos da estrutura regulatória para o

acesso expandido/uso compassivo" e "ética no uso de medicamentos sem registro" e as principais palavras-chave foram: acesso expandido, eficácia, segurança, COVID-19, risco, autorização emergencial, dados de mundo real. **Conclusões:** A regulação de medicamentos sem registro merece ser melhor explorada por estudos, de qualidade, na área da Saúde Coletiva, e em países do sul global, com pesquisas que se debrucem em torno da construção dos elementos da proteção da saúde individual e coletiva na regulação de medicamentos sem registro.

PALAVRAS-CHAVE: Regulação e Fiscalização em Saúde; Registro de Medicamentos; Brasil; Estados Unidos; Europa

INTRODUCTION

The use of unregistered medicines points to a change in the regulatory paradigm for innovative medicines by shortening access to medicines still in the experimental phase, which also increases uncertainties about the risks related to the use of these drugs[1]. This constitutes a relevant discussion and a paradox in itself, since the social transformation of the molecule into a medicine derives, in the traditional model, from the health assessment of the risks and benefits of these products for individual and collective health[2].

Driven by pressure from patient groups for access to promising drugs, especially since the human immunodeficiency virus (HIV) epidemic in the 1980s, regulatory agencies have created regulatory instruments to allow early access to drugs not yet registered, in cases of unmet medical need[3].

Access to unregistered medicines has added issues to the regulatory task, such as: the possible discrediting of regulatory action by the increase in drug safety problems, difficulties in recruiting patients for randomized clinical trials, interruptions in the supply of drugs for clinical trials, the risk of capture of the regulatory institution by the pharmaceutical industry, as well as the low perception of risk-benefit by the patient[4,5].

The regulation of unregistered medicines is therefore considered to be a debate that involves international coordination between regulatory agencies and ethical, political, and technical issues that can influence the regulatory processes adopted by countries[5].

Studies in different countries have sought to discuss the issue, which involves disputes of interest between public health and the pharmaceutical market[6,7,8,9]. As this is a complex subject which has been growing in interest in the scientific community, the question is: what are the main characteristics of scientific production on the health regulation of unregistered medicines?

To date, no publications on trends in bibliographic production on the subject have been found in scientific literature. The aim of this study was therefore to carry out a bibliometric analysis to identify the characteristics of scientific production on the regulation of unregistered medicines, considering the existence of regulatory agencies of varying degrees of maturity in the countries and regions selected: Brazil, the United States, and Europe.

This study is considered relevant because it makes it possible to systematically map the research carried out and identify any gaps in knowledge on the subject. In addition, the results could help support the formulation of regulatory policies and decision-making in a context that is tending towards regulatory harmonization between countries.

METHOD

This is a descriptive bibliometric analysis of scientific production on the regulation of unregistered medicines in Brazil, the United States, and Europe.

Bibliometric analysis derives from librarianship and has been used frequently in the health sciences[10]. It allows the measurement of indices of production and dissemination of knowledge, as well as monitoring the development of scientific areas. It analyzes different types of material: books, theses, scientific articles, communications in proceedings, texts, or databases[10]. Bibliometric studies can involve indicators such as scientific quality, scientific impact, scientific activity and thematic associations[10]. The last two indicators were used in this study.

The study was limited to Brazil, the United States, and Europe, which have regulatory agencies belonging to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and which are references for the Brazilian health authority.

The following exclusion criteria were adopted for the research: no relevance to the study's objective; unavailability of the full article; research that did not involve Brazil, the United States, and/or Europe; clinical studies; studies focusing on specific medicines, except for searches involving the descriptor "emergency use authorization"; discussion of off-label use of medicines or accelerated registration of medicines; duplicates; articles in press; and documents classified as books or regulatory agency guides.

Articles in Portuguese and English were collected from the Scientific Electronic Library Online (SciELO), *Portal da Capes* (Coordination for the Improvement of Higher Education Personnel), and Web of Science databases, with no time frame or filters.

The search used the terms "compassionate use trials"; "expanded access"; "*uso compassivo*"; "emergency use authorization";

"regulatory framework"; "safety"; "early access"; "medicines"; "*medicamentos*"; "Brazil" and "UK" combined in different ways using the Boolean operator "AND". When necessary, quotation marks were used to delimit the search. Examples of search strategies in the Web of Science database: "expanded access" AND "regulatory framework" or "early access" drugs AND "UK". The descriptors were defined based on the Dictionary of Health Sciences Descriptors (DeCS) and the keywords most commonly used in scientific literature.

At first, the descriptor "UK" was used to collect data on scientific production on the regulation of unregistered medicines in the United Kingdom. However, because the largest number of articles that met the eligibility criteria for this descriptor referred to Europe, the analysis was directed to the European region.

When screening the articles, we tried to identify the descriptors in the titles and abstracts, as well as the inclusion and exclusion criteria. After purging articles that were not in line with the aim of the study, the articles selected after screening were fully read, which led to the exclusion of other articles that were also not in line with the eligibility criteria. Both stages, screening and floating reading, were carried out by the first author. Figure 1 systematizes the process of selecting articles for bibliometric analysis.

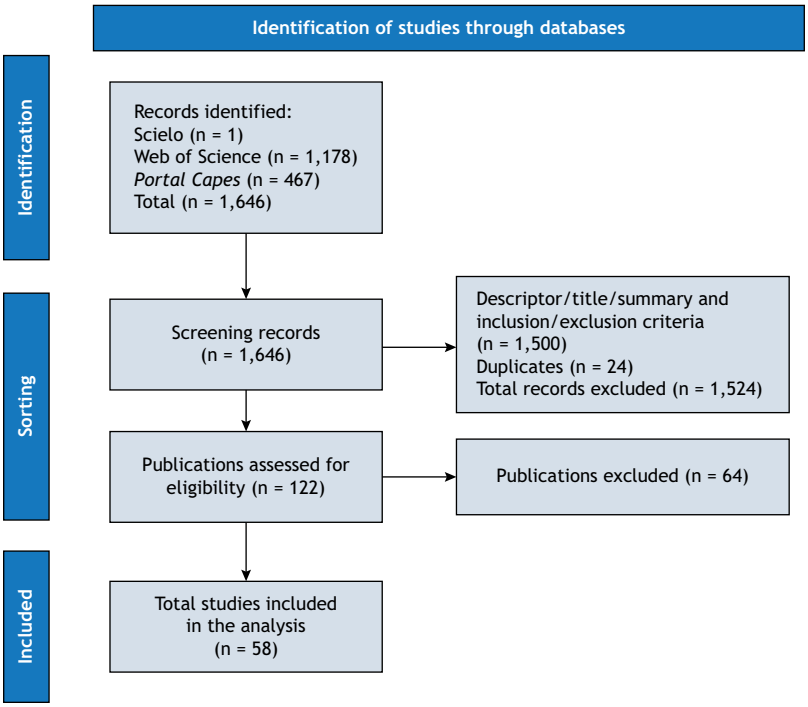
A data extraction matrix was used for bibliometric analysis, created using the Microsoft Office Excel® software, version 2019, containing the following categories: year of publication; type of publication; area of knowledge related to the article; journal; region of affiliation of the authors; country of the study; type of research/methodology; thematic focus of the publication. The classification of the theme of each publication was based on the objectives and/or abstracts of each study. The data was collected in January and February 2023.

For the quantitative descriptive analysis, the absolute and relative frequencies and averages of the data related to the categories used were calculated.

The VOSviewer® software was used to describe the main keywords related to the topic of regulation of unregistered medicines in this study. To establish this overview, a search was made in the Web of Science database, compatible with this program, as it corresponds to the database with the largest number of articles identified and collected.

To define the area of knowledge of each article, it was necessary to examine the scope of the scientific journals on their respective websites. The areas were organized according to the classification defined by the National Council for Scientific and Technological Development (CNPq).

It should be noted that the articles classified by the journals as "Ethical research", "Analytical report", and "Special report" were categorized in this study as "Other", as they did not fit into the other classifications (original article, review article, opinion article, and editorial), according to the specification given by the journal.



Source: Adapted from the PRISMA 2020 Flowchart[11].

Figure 1. Flowchart of the process of identifying and selecting the scientific publications included in the bibliometric analysis of the regulation of unregistered medicines in Brazil, the United States, and Europe.

RESULTS

For the bibliometric analysis, 58 scientific articles were selected. Thirty-four articles came from the Web of Science database, 23 from the *Portal da Capes*, and only one from the SciELO platform. The number and distribution by year of scientific publications are shown in Figure 2.

The bibliometric study showed that the first publications on the subject appeared from 2008 onwards and remained constant and variable in quantity, except in 2012 and 2013. In these years the articles may have been suppressed by the inclusion/exclusion criteria used in the study.

An average of 4.5 articles per year was observed, as well as an increase in publications in 2016 and 2017 and from 2020 onwards. It should be noted that part of the scientific productions found from 2020 onwards (n = 10) discussed access to unregistered medicines based on regulatory instruments aimed at public health emergencies, due to the pandemic caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus[12,13,14].

The most frequent types of publication were original articles (n = 23; 39.65%) and opinion articles (n = 18; 31.03%). Other types of publications found were review articles (n = 11; 18.96%), editorials (n = 2; 3.45%), and articles categorized as "Other" (n = 4; 6.89%).

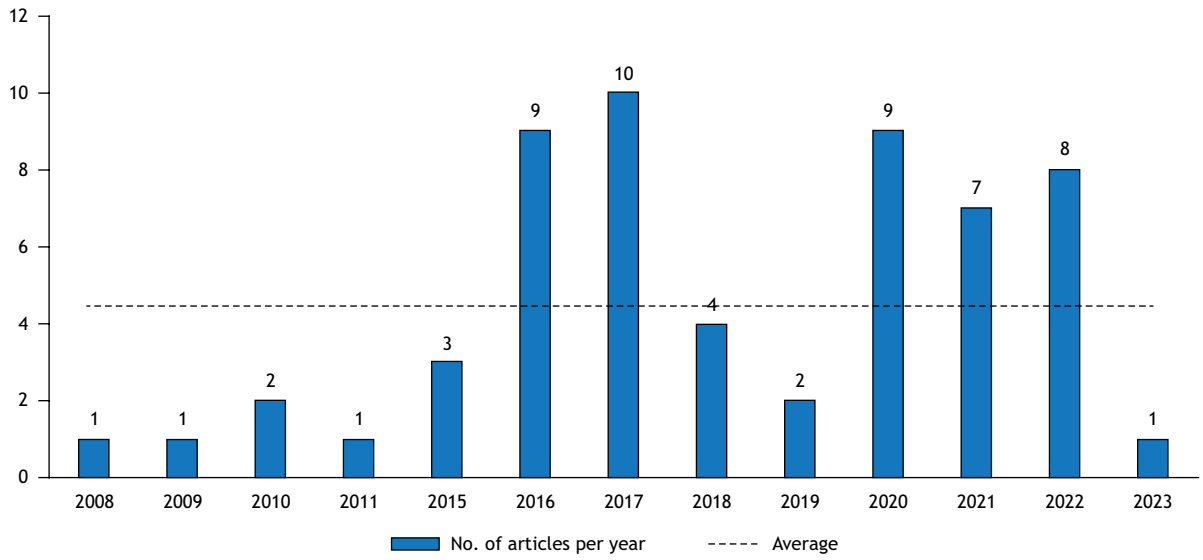
In the selected publications, the issue of regulating unregistered medicines was discussed predominantly in the United States (n = 36), followed by Europe (n = 12). Only four articles included Brazil and focused on safety in the use of unregistered medicines[15], aspects of regulatory action in access to unregistered medicines[13], and aspects of the regulatory structure for access to unregistered medicines[7,16].

The United States proved to be the main region of affiliation of the authors who published on the subject (n = 27), followed by the United Kingdom (n = 7).

Most of the articles did not describe the type of research and, in general, did not present a methodology (n = 38; 65.52%). From what could be identified from reading the papers, most were descriptive studies (n = 16; 27.59%); two articles were defined by the authors as cross-sectional studies (3.45%), and one publication corresponded to a systematic review (1.72%).

It should be noted that six publications, representing 10% of the articles collected, declared conflicts of interest with the pharmaceutical industry. Two, published in different journals and in different years, reported the same pilot experience on the subject of "Using external evaluation to promote access to unregistered medicines"[17,18].

The objectives of the studies that declared conflicts of interest with the pharmaceutical industry were: 1) "to present eight key regulatory framework factors to facilitate patient access to compassionate use of medicines"[19]; 2) "to present a particular industry's new strategy for using information collected in compassionate use drug refills as a source of real-world data on drug efficacy"[20]; 3) "present a pilot of a partnership between a pharmaceutical industry and a medical school to establish and evaluate the use of an independent, external, expert committee in ensuring compassionate access to experimental medicines in a transparent, fair, beneficial, evidence-based, and patient-centered manner"[17]; 4) "present a pilot of a partnership between a pharmaceutical industry and a medical university to form a compassionate use advisory committee and provide recommendations on access to oncology drugs"[18]; 5) "discuss the impulse to rescue individual patients facing terrible diseases and emphasize the ethical issues related to such efforts"[21]; and 6) "to provide an overview of the regulatory approaches adopted during the beginning of the pandemic, an assessment of the trends observed and some reflections and proposals to leverage learnings and opportunities"[12], referring



Source: Own elaboration based on the search carried out in the *Portal da Capes*, SciELO, and Web of Science (2023) databases.

Figure 2. Distribution of the number of publications on the regulation of unregistered medicines in Brazil, the United States and Europe, 2008-2023.

to an article published in 2021, when the pandemic caused by the SARS-CoV-2 virus was underway.

The scientific publications selected were distributed according to area of knowledge and period of publication (Table 1).

There was a concentration of journals in the broad area of Health Sciences, sub-area "Medicine" (n = 53; 91.38%), with a diversity of scope among the journals. Only a few papers were published in Collective Health (n = 4; 6.94%) and only one in Human Sciences, philosophy.

In all, 16 thematic categories were identified into which the articles were grouped, which demonstrated the diversity between scientific publications on the regulation of unregistered medicines in Brazil, the United States, and Europe (Table 2).

Table 1. Distribution of articles according to area of knowledge and journal, following criteria defined by the CNPq.

Major area of knowledge	Specific areas	Journal	N	%
Health Sciences	Medicine	JAMA Network Open	1	1.72
		Therapeutic Innovation & Regulatory Science	11	18.97
		Pharmaceutical Medicine	2	3.45
		Clinical Therapeutics	1	1.72
		Journal of Law Medicine and Ethics	1	1.72
		JAMA	2	3.45
		Frontiers in Oncology	1	1.72
		Frontiers in Pharmacology	3	5.17
		JAMA Health Forum	1	1.72
		Journal of Medical Ethics	1	1.72
		Clinical and Translational Science	1	1.72
		Expert Opinion on Investigational Drugs	4	6.90
		British Journal of Clinical Pharmacology	3	5.17
		Life	1	1.72
		BMC Health Services Research	1	1.72
		PLOS One Medicine	1	1.72
		The AAPS Journal	1	1.72
		The Journal of Medicine Access	2	3.45
		BMC Medical Ethics	3	5.17
		Regenerative Therapy	1	1.72
		TRIALS	2	3.45
		European Journal of Internal Medicine	1	1.72
		Perspectives in Biology and Medicine	1	1.72
		Journal of Pharmaceutical Policy and Practice	1	1.72
		JACC: Basic to Translational Science	1	1.72
		Humanities and Social Sciences Communications	1	1.72
		The Journal of Clinical Pharmacology	1	1.72
		British Pharmacological Society	1	1.72
		Journal of Business Ethics	1	1.72
		Expert Opinion on Pharmacotherapy	1	1.72
		Subtotal	53	91.38
	Collective Health	Science & Collective Health	2	1.16
		Pan American Journal of Health	2	1.16
		Subtotal	4	6.90
Humanities	Philosophy	Journal of Medicine and Philosophy	1	0.58
		Subtotal	1	1.72
Total			58	100

Source: Prepared by the authors, 2024.

The topics most covered in the articles were "Aspects of the regulatory framework for expanded access/compassionate use" and "Ethics in the use of unregistered medicines".

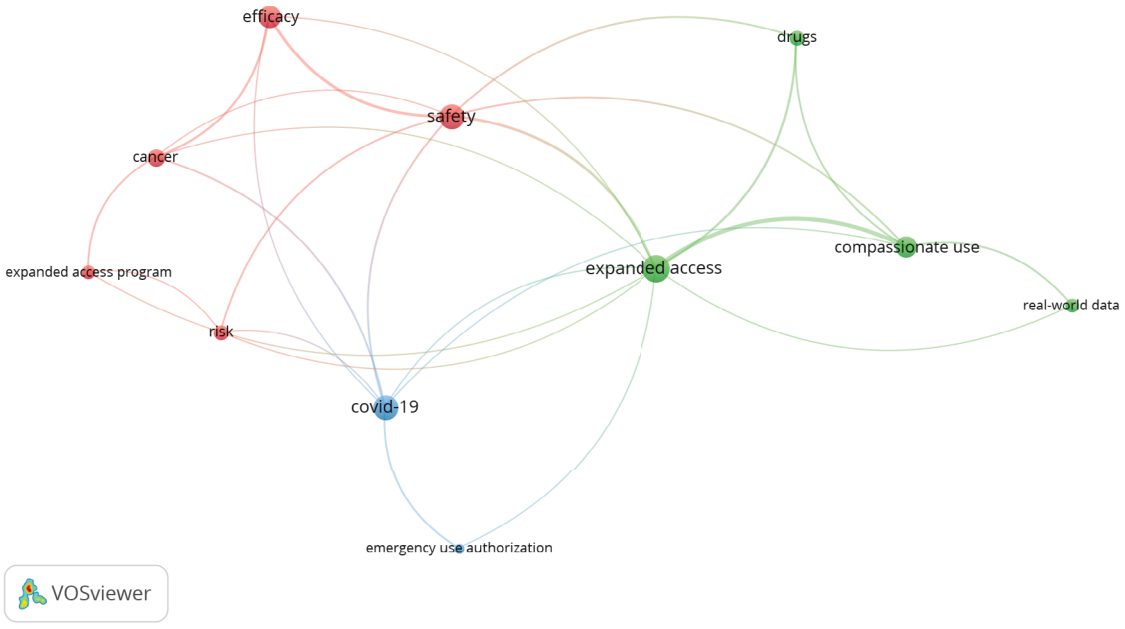
The main keywords, correlated by frequency x theme, contained in the research on the regulation of unregistered medicines were: expanded access, efficacy, safety, COVID-19, compassionate use, medicines, cancer, real-world data, expanded access program, risk, and emergency authorization (Figure 3).

Figure 3 shows the formation of three thematic clusters associated with the main keywords. One of them refers to the keywords

Table 2. Main topics covered by scientific research into the regulation of unregistered medicines in Brazil, the United States, and Europe.

Thematic category	N	(%)
Access to unregistered medicines	4	6.90
Aspects of regulatory action in access to unregistered medicines	3	5.17
Aspects of the regulatory framework for expanded access/compassionate use	14	24.14
Ability to pay for access to unregistered medicines	1	1.72
Physicians' understanding of expanded access/compassionate use programs	2	3.45
Definitions of terms used in the authorization of unregistered medicines	2	3.45
Effectiveness of unregistered medicines	1	1.72
Strategies for making the regulatory structure more flexible for access to unregistered medicines	2	3.45
Ethics in the use of unregistered medicines	7	12.07
Ethics and regulatory framework	3	5.17
Operation of the expanded access/compassionate use program	6	10.34
History of the compassionate use of a medicine	1	1.72
Pharmaceutical industry and unregistered medicines	4	6.90
Production of scientific evidence through expanded access/compassionate use	4	6.90
Safety of unregistered medicines	2	3.45
Use of external scientific evaluation to promote access to unregistered medicines	3	5.17

Source: Prepared by the authors, 2024.



Source: Prepared from a search of the Web of Science database (2023), using the VOSviewer® software.

Figure 3. Distribution of the main keywords used in research on the regulation of unregistered medicines in Brazil, the United States, and Europe, by frequency and thematic grouping.

"emergency use authorization" and "COVID-19"; other groups together the keywords "efficacy", "safety", "risk", "cancer", and "expanded access", while the keywords "medicines", "compassionate use", "expanded access", and "real-world data" form another grouping.

DISCUSSION

This study has shown that scientific production on the health regulation of unregistered medicines is recent, with an increase in publications from 2016 onwards, when the number of studies was above average, followed by a new increase after 2020. It is possible to deduce that reflections on the subject have become increasingly relevant to researchers, especially after the pandemic caused by the SARS-CoV-2 virus.

The high number of opinion articles and methodologically undefined publications identified in this bibliometric analysis shows the need for more in-depth studies to understand the phenomenon.

The topic of health regulation of unregistered medicines was less prominent in the areas of Collective Health and Human Sciences, since the publications were concentrated in specialized journals, which suggests that the topic has been debated primarily from a technical perspective.

The complexity of drugs as an object of health[22], coupled with the social cost caused by the lack of medicines for unmet health needs, and the possible negative impact on the population's health of access to drugs with limited efficacy and safety data, point to a range of discussion topics to be explored by Collective Health. This is because Collective Health is understood as a scientific field and sphere of practice that enables an understanding of health and its social determinants, with the aim of promoting, protecting, and recovering the health of the community[23].

It is noteworthy that the majority of the scientific production selected was carried out in the United States, the country that began regulating access to unregistered medicines, having created the expanded access program in 1987 in response to pressure to speed up the approval of drugs in the human immunodeficiency syndrome epidemic [4,24]. The small number of studies in Brazil means that little information on the subject is available to the scientific community, despite the fact that the country has been regulating programs for expanded access to medicines since 1999[25].

The number of scientific publications declaring conflicts of interest with the pharmaceutical industry was noteworthy. It was noted that all the objectives of these articles worked, from different perspectives, with proposals to contribute to and stimulate the reduction of regulatory barriers. The papers discussed bottlenecks related to regulatory decision-making in drug approval and most of them even involved new ways of facilitating the approval of unregistered drugs.

Reducing regulatory barriers is in the interest of the pharmaceutical industry which, as a science-based oligopoly that differentiates itself in the market through marketing and innovation[26], depends on the rapid introduction of new drugs to the market to remain competitive. Drug regulation is a complex task that seeks to balance public health priorities and market interests[27] and access to unregistered drugs involves a dispute of interests between various players such as the pharmaceutical industry, patient groups, prescribers, the scientific community[28], and regulators.

The pharmaceutical industry has invested in high-cost drugs for unmet medical needs, such as oncology and orphan drugs[29,30], which make up the profile of drugs approved in expanded access programs[31].

The case study of the drug gefitinib, indicated for lung cancer, for example, showed how the reports of patients, chosen by the manufacturer of the product, who used the drug in expanded access programs, influenced the advisory board of the Food and Drug Administration (FDA) to suggest the approval of the drug, which was carried out by the agency, even though the efficacy and safety data did not correspond to the technical-scientific criteria of the health authority[32].

In this way, it can be seen that the pharmaceutical industry acts, directly or indirectly, to encourage access to promising drugs, seeking to facilitate regulatory approval.

The existence of scientific papers showing conflicts of interest with this sector may suggest yet another way in which the pharmaceutical industry is influencing regulators in order to make the regulation of innovative drugs more flexible, given that the health risk assessment and management policies carried out by health regulatory agencies are based on the scientific knowledge produced[33]; and publications in scientific journals are sources of this knowledge.

The most recurrent themes on the regulation of unregistered medicines were "Aspects of the regulatory structure for expanded access/compassionate use" and "Ethics in the use of unregistered medicines". Regarding the first theme mentioned, some studies have shown a tendency for health regulations to become more flexible in order to facilitate access to innovative medicines[34,35]. Others have shown the existence of discrepant differences in the regulatory processes adopted by countries for the use of unregistered medicines, although in a context of calls for regulatory harmonization, highlighting concerns about the protection of individual and collective health[7,8,36,37,38].

The discussion on "Ethics in the use of unregistered medicines" has proved to be a major challenge, since it raises relevant questions regarding the defense of the patient's individual right to decide on the risks they would be willing to undergo in the face of a new treatment, as well as the need to observe the bioethical principles of non-maleficence and beneficence in the use of medicines, since the perception of risk in sick patients is low and the use of unregistered medicines involves limited access to data of ethical and health importance, such as the efficacy and safety of medicines[4,39,40,41].

Although these are attributes that are highly problematized in the use of unregistered medicines, few studies have focused directly on the efficacy and/or safety of these medicines, even though these terms appeared with high frequency among the keywords of the selected studies[15,42,43].

This is relevant, as some studies have shown that around 25% of the drugs used in compassionate use/expanded access programs have not received regulatory approval[44], in addition to the occurrence of serious adverse reactions[15] or difficulties in distinguishing between adverse events and disease progression during the use of unregistered drugs[45]. However, one study claimed not to identify adverse reactions with fatal or harmful drugs for the development of expanded access programs[46].

In other words, in addition to the low production, the existing studies on the efficacy and safety of unregistered medicines have revealed controversial results that make it difficult to form an opinion, demonstrating a gap in the knowledge of this fundamental parameter in the risk-benefit assessment of a medicine[47]. The relevance of the focus on the efficacy and safety of medicines stems from the fact that these are not exclusively technical aspects; they are attributes inherent to the medicine, which make it a social good, as they are directly related to the regulatory function of protecting health[22].

The grouping of keywords, shown in Figure 3, revealed that research on the regulation of unregistered medicines was distributed according to the paradox inherent in the theme of *risk vs. access*. In this sense, one group of studies could highlight the increased health risk associated with the use of unregistered medicines, while another would emphasize the possibility of information produced in interventionist studies, such as expanded access, being used as scientific evidence to collaborate with access to innovative therapies[44,45].

In the articles in this study, some authors[34] defended the importance that expanded access programs have had in producing real-world data, which supported or complemented information for the approval of drugs by the EMA and FDA in 2019. On the other hand, emphasis has also been placed on the need to be careful when defending the use of expanded access programs as "real-world evidence" to attest to the safety and quality of medicines, since the reliability of the data produced in these programs can be debatable[44].

In addition, the studies that used the keyword "emergency use authorization" for medicines were directly related to COVID-19, as this was a strategy for accessing unregistered medicines that was widely used during the pandemic, although the use of unregistered medicines through the regulatory route of expanded access[12,13,14,34].

Although the analyses in this study were limited to certain countries and one region, it was possible to observe that the issue of regulating unregistered medicines has been given more attention in central countries. The non-inclusion of studies focused on the use of specific medicines in compassionate use and expanded access programs may have limited the identification of studies on the safe use of unregistered medicines. In addition, few studies were identified on the safety profile of unregistered medicines, which highlights the need for further research to better understand the growing phenomenon in the current context of regulating unregistered medicines.

CONCLUSIONS

This study showed that the concentration of publications in the United States and Europe and the low production on the subject in Brazil confirm the need to expand studies on the regulation of unregistered medicines in this country, taking advantage of the growing interest of the scientific community.

There was a scarcity of studies with a more analytical focus and in areas other than the medical field, which explored a broader and less technical view of the issue. Despite this, the paradox between access, as a right to health, and minimizing risk, as an element of health protection, is so relevant to the issue of regulating unregistered medicines that it is evident in the distribution of keywords in the publications included.

The greater thematic focus on aspects of the regulatory structure for expanded access/compassionate use, from a more technical perspective addressed by the scientific publications, did not seem sufficient to deepen the understanding of the nuances inherent in the regulation of unregistered medicines from the perspective of guaranteeing health protection in the face of market interests, which were pointed out by the identification of bibliographic productions containing conflicts of interest with the pharmaceutical industry.

It is recommended that studies be carried out to produce knowledge on the efficacy, safety, and regulatory assessment of innovative drugs released for use without registration, as well as on the safety of these drugs used outside clinical trials. It is important to produce knowledge about the motivations behind the formulation of regulatory frameworks for the use of unregistered medicines in different countries, with a view to understanding the regulation of medicines as a strategic axis for achieving the rational use of drugs, as long as it is centered on health needs and not just on market logic.

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Authors' Contributions

Cardoso AST, Costa EA - Conception, planning (study design), data acquisition, analysis, interpretation, and writing of the paper. All the authors approved the final version of the paper.

Conflict of Interest

The authors declare that there is no potential conflict of interest with peers and institutions, political or financial, in this study.